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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/735,995	12/14/2000	Mark Keating	2323-156	6821

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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	7

DATE MAILED: 06/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/735,995	KEATING ET AL.	
	Examiner	Art Unit	
	Celine Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-18,22-25,29 and 30* is/are pending in the application.

4a) Of the above claim(s) *11-18,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Notice of References Cited	Application/Control No. 09/735,995	Applicant(s)/Patent Under Reexamination KEATING ET AL.	
	Examiner Celine Qian	Art Unit 1636	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Wall, Transgenic livestock: Progress and prospects for the future, 1996, THERIOGENOLOGY, Vol. 45, pp. 57-68
	V	Wang et al., The molecular basis of long QT syndrome and prospects for therapy, 1998, MOLECULAR MEDICINE TODAY, pp. 382-388
	W	Nakajima et al., Novel mechanism of HERG current suppression in LQT2 shift in voltage dependence of HERG inactivation, 1998, CIRC. RES., Vol. 83, pp. 415-422
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

DETAILED ACTION

Claims 11-18, 22-25, 29 and 30 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group III in Paper No. 6 is acknowledged. The traversal is on the ground(s) that a search of all the mutants will not be burdensome because they have similar structure and same utility. In addition, Applicants argue that a search of all the mutants were done in the parent case. This is not found persuasive because 1) each application is examined on its own merits; 2) amino acid sequence encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Applicant's claimed sequences comprise different mutations including addition, deletion and substitution that may result in protein with different structure and function (the specification does not provide evidence that all the mutated protein/polypeptides have same structure and functional property). Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Accordingly, in most cases, only one (1) independent and distinct nucleotide sequence will be examined in a single application without restriction. Therefore, a search of the entire list of mutants will be burdensome to this office.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 11-18, 29 and 30 are withdrawn from examination for being directed to non-elected subject matter. Claims 22-25 with respect to mutation Cys 572, Asp 588, Val 614, Ala 630 and Leu 29 are currently under examination.

Priority

This application claims priority to application 09/226,012 filed on 1/06/1999, the priority date is granted. This application also claims priority to application 09/122,847 filed on 7/27/1998. This priority date is only granted to claims which recite mutation Cys 572, Asp 588, Ala 630.

Claim Objections

Claims 22-25 are objected to for containing non-elected subject matter. For example, claim 22 contains the limitation of a mutation shown in Table 7 (encompassing 69 mutations), however, Applicant has elected 5 specific mutations. Amending the claims such that they are only directed to the five elected mutations is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is a method to screen for drugs which are useful in treating a person with either of 5 mutations recited in claim 22, comprising measuring induced K+ current in cells either expressing wild type HERG or mutant HERG, adding a drug to the cells expressing mutant HERG and measuring K+ current again, wherein a restoration of K+ current to levels found in cells expressing wild type HERG after drug addition indicates that the drug is useful in treating patients with mutation in HERG.

The state of art at the time of filing teaches that mutations in HERG, a cardiac K+ channel with six trans-membrane domains, are linked to LQT2 syndrome by linkage studies (see Wang et al., 1998, Molecular Medicine Today, September issue, pages 382-388). Specific mutations within HERG have been confirmed to cause LQT2 syndrome, for example, a single base pair deletion (ΔT1671), a stop codon mutation (T611 stop) and a missense mutation (A561T) (see page 384, 2nd col., 3rd paragraph). Wang et al. further teach that electrophysiological studies of five LQT-associated specific mutations (see page 387, Figure 3a) in HERG have been shown to act through a loss of function or a dominant-negative mechanism (see page 385, 1st col., 1st paragraph and Figure 3a). However, the art does not teach that specific mutations in HERG comprising 29L, 572C, 588D or 630A causes LQT syndrome or loss of K+ function in electrophysiological studies. The prior art only teaches that mutation at 614V resulted in loss of HERG K+ channel function in oocytes injected with mutant HERG cDNA (see Nakajima et al., 1998, Cir. Res. Vol 83, pages 415-422). Therefore, it is not known in the art whether the four other mutations as claimed would result in any abnormal phenotype, in other

words, loss of the HERG function or alteration in K+ channel conductance. If these mutations do not produce a change in K+ channel conductivity, then the method as claimed is not enabled. The claimed method is only enabled for the mutation that causes a K+ current change when expressed in a cell, 614V. Absent teaching from the art, one skilled in the art would have to turn to specification for guidance to practice said invention.

The breath of the claims is broad. The claims encompass a drug screen method by measuring and comparing K+ current in cells expressing wild type or mutant HERG that include either one of the mutation recited in claim 22. The claims also encompass said drug screen method wherein the cells expressing wild type or mutant HERG is obtained from a transgenic animal.

Because the claims encompass using non-human transgenic animal cells comprising specific mutations, there is added unpredictability to the enablement of the method. The successful generation of transgenic animal comprising said mutant HERG gene in the genome with a specific phenotype (altered K+ channel current in all cells of said animal) is essential to the enablement of the method as claimed. However, at the time of filing, the state of art with regard to producing transgenic animal with a specific phenotype is considered unpredictable. Not only the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68), the particular genetic elements required for optimal expression also varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). The specification fails to teach a method of generating any transgenic animal with altered K+

current in its cells. Therefore, in the absence of specific guidance and working examples, the production of transgenic animals with the phenotypes that is required for the enablement of the claimed method is unpredictable. Otherwise, the method of screening drugs by comparing K+ currents in cells (not from the transgenic animal) expressing 614V mutant HERG and wild type HERG is enabled.

The guidance provided in the specification is very limited. The specification only discloses that said mutations are discovered by SSCP analysis in patients with LQT syndrome (see page 77, 2nd paragraph). However, the specification does not disclose whether these mutations cause a specific phenotype (especially with regard to K+ current) in cells expressing said mutants or transgenic animals expressing said mutant. The specification also fails to teach how to determine which mutation causes a loss of HERG function or alteration of K+ conductance. The specification also fails to teach a nexus between restoring K+ conductance or HERG function and the amelioration of LQT. Without the teaching from the specification, one of skilled in the art would have to engage in undue amount of experimentation to practice the method as claimed. Therefore, the specification is not enabled for the method of screening drugs as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "bathing solution" renders the claims indefinite because it is unclear what is the content of the solution. In other words, is the solution for bathing or a media for cell proliferation?

The term "more similar" is a relative term which renders the claim indefinite. The term "more similar" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how much "more similar" the K+ current has to be to determine that the drug is useful.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al (1998, Mol. Medicine Today, September 382-388), in view of Nakajima et al (1998, Cir. Res. Vol 83, pages 415-422) (in so far as the claims read on the specific mutation V614).

The claims are drawn to a method of screen drugs which are useful in treating a patient with a mutation in HERG which result in a valine at amino acid 614, comprising measuring induced K+ current in cells either expressing wild type HERG or mutant HERG, adding a drug to the cells expressing mutant HERG and measuring K+ current again, wherein a change in K+ current in cells expressing mutant HERG close to cells expressing wild type HERG after drug addition indicate that the drug is useful in treating patients said mutation in HERG.

Wang et al. teach that mutations in HERG, a cardiac K+ channel with six trans-membrane domain, are linked to LQT2 syndrome by linkage studies (see page 384, 2nd col., 3rd paragraph). Wang et al. also teach that this specific mutation within HERG has been confirmed to cause LQT2 syndrome. Wang et al. further teach that electrophysiological studies of five LQT-associated mutations in HERG has been shown they act through a loss of function or a dominant-negative mechanism (see page 385, 1st col., 1st paragraph). In addition, Wang et al. teach that based upon the electrophysiological finding that elevation of K+ concentration increased in outward K+ current, specific therapy comprising elevating serum K+ concentration is developed for patients of LQT with HERG mutation and resulted in shortened QT interval in some patients (see page 387, 1st col., 4th paragraph, lines 9-16). However, Wang et al. do not teach a method of screening drugs to treat patients with 614-valine mutation in HERG by measuring and comparing K+ current in cells expressing wild type and mutant HERG.

Nakajima et al. teach that specific mutation including T474I, A614V, and V630L in HERG gene resulted in loss of the function of the HERG gene. Nakajima et al. teach that electrophysiological study demonstrate that injection of mutant cDNA to Xenopus oocytes do not generate any K+ current (see page 417, 1st col., 2nd paragraph, and Figure 3). Nakajima et al. also teach that co-injection of wild type plus mutant cDNA of HERG to Xenopus oocytes resulted in reduced K+ current comparing to injection of wild type cDNA alone (see page 417, 2nd col., 1st paragraph, and Figure 4), suggesting the mutant HERG suppresses the K+ channel in a dominant-negative manner.

It would have been obvious to one of ordinary skill of art to develop a drug screen method by measuring and comparing K+ current in cells expressing wild type or mutant HERG (614V). The ordinary artisan would have been motivated to do so because of the teaching of Wang et al., who teach that therapies targeting HERG K+ channel are developed and proved partially effective in treating LQT, a HERG associated disease. Nakajima et al. further provide a method of measuring K+ in Xenopus oocytes injected with wild type or mutant HERG. In addition, Nakajima et al. confirm the mutation at amino acid 614 to valine results in loss of function of HERG as a K+ channel, and act as dominant-negative suppressor to wild type HERG. As such, the ordinary artisan would have reasonable expectation of success by combined teaching of Wang et al. and Nakajima et al., adding an agent that result in increased concentration of K+ to cells expressing 614V mutant HERG alone or with wild type HERG would increase the K+ channel conductivity, wherein said agent is useful in treating patients with 614V mutation if the K+ current is increased. Therefore, the invention as claimed would have been prima facie obvious to one of ordinary skill of art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
June 17, 2002

JAMES KETTER
PRIMARY EXAMINER